American Pain Society

RESEARCH
EDUCATION
TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 16, No 12 (December), 2015: pp 1300-1311
Available online at www.jpain.org and www.sciencedirect.com

Treatment of Postherpetic Neuralgia With Gastroretentive Gabapentin: Interaction of Patient Demographics, Disease Characteristics, and Efficacy Outcomes

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Abstract: **To understand how patient demographics and patient-reported disease characteristics relate to successful management of postherpetic neuralgia (PHN), integrated data from phase 3 and phase 4 studies of patients with PHN (n = 546) who received once-daily gastroretentive gabapentin (G-GR, 1800 mg) were analyzed. There were widespread, networked, positive correlations among efficacy end points—pain qualities on the visual analog scale (VAS) and Brief Pain Inventory (BPI), measures of pain interference on the BPI, and Patient Global Impression of Change (PGIC)—most likely characterized by positive feedback loops, in which pain interferes with patient functioning, and poor functioning enhances pain. VAS scores at baseline or at week 2 were the strongest predictors of being "much" or "very much" improved on the PGIC; BPI sleep interference scores were the strongest predictors of percent changes in BPI pain qualities and in the average of BPI interference scores, whereas age, sex, and race were not important predictors. In addition to VAS, BPI sleep interference and PGIC assessments appeared to be key co-strategic factors important for successful treatment outcomes, and should be considered as co-primary end points in future clinical trials of PHN. This could improve detection of true positive efficacy responses and guide successful transition to real-world clinical practice.**

Perspective: ***This study describes complex relationships among measures of pain intensity, pain interference with daily activities, and demographics of patients with PHN treated with G-GR. Such comprehensive characterization provides important insight into how different variables contribute to successful treatment, and may lead to better management of neuropathic pain.***

Key words: *Postherpetic neuralgia, neuropathic pain, gabapentin, gastroretentive, pain intensity, pain interference.*

Reactivation of dormant varicella zoster virus, originally contracted in childhood during a chicken pox infection, leads to herpes zoster (or shingles), a painful skin rash with blisters.[19,45] The symptoms of herpes zoster typically resolve within 2 to 4 weeks, but approximately 10 to 20% of patients develop postherpetic neuralgia (PHN), a neuropathic pain condition.[11,28,31,44] PHN is commonly defined as pain persisting for more than 3 months after the healing of the herpes zoster rash, although it can persist for more than a year.[44] Recommended first-line treatment options for PHN include gabapentinoids (various formulations of gabapentin and pregabalin), tricyclic antidepressants, and the topical lidocaine 5% patch.[2,5,13] The gastroretentive formulation of gabapentin (G-GR), approved by the US Food and Drug Administration (FDA) for treatment of PHN, uses a polymer-based technology to swell when the tablets come in contact with gastric fluid, and is retained in the stomach for 8 to

Received March 31, 2015; Revised July 28, 2015; Accepted August 11, 2015.
This study was funded by Depomed, Inc, Newark, CA. I.B. is an employee and shareholder of Depomed, Inc.
The authors have no further conflicts of interest to declare.
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
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1526-5900

http://dx.doi.org/10.1016/j.jpain.2015.08.011

10 hours,[1,16] allowing for once-daily dosing and a simple 2-week titration regime. In 2 phase 3 placebo-controlled studies and in 1 phase 4 open-label study, once-daily 1800 mg of G-GR provided significant pain relief, significantly reduced pain interference with daily activities, and demonstrated a good safety and tolerability profile in patients with PHN, including in older patients.[12,25,37,43]

Available treatments for PHN focus on shortening the duration and severity of the pain. However, neuropathic pain associated with PHN can be debilitating, and it frequently interferes with patients' physical and social functioning.[4] Therefore, in addition to pain relief, improvement in various aspects of pain interference with patients' daily lives may provide quality patient care and improve patients' overall well-being. Several instruments that measure the effect of treatment on pain intensity and on other pain qualities, as well as on how pain affects various aspects of patients' lives, have been developed and are commonly used in clinical studies of pain therapies.[7] Among these, the visual analog scale (VAS) is among the most frequently used instruments to measure pain intensity.[14] The Brief Pain Inventory (BPI) measures both the intensity of pain (worst, least, average, and current pain) and the interference of pain in 7 aspects of patient's functioning (general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life).[3] The Patient or Clinical Global Impression of Change (P/CGIC) is commonly used to assess overall efficacy and treatment experience.[22]

Pain intensity is the most common primary outcome variable assessed in studies of pain therapies, including in PHN, whereas measures of patients' quality of life and how pain interferes with their functioning are secondary efficacy measures. Because pain frequently interferes with daily activities, measures of pain intensity would be expected to be positively associated with measures of pain interference with patient functioning. Levels of pain intensity and its interference recorded at baseline may influence the effectiveness of treatment. Also, the complexity of pain and its interference with functioning is largely dependent on subjective reporting by patients, and patient demographics (ie, age, sex, or race) may influence self-reporting. Moreover, age, sex, and race have been reported to be differentially associated with the experience of pain,[8,26,34] which may also influence treatment outcomes.

A major risk factor for PHN is advanced age, with approximately half of all PHN cases occurring in patients older than 60 years, and female sex has been reported to be an important risk factor among others.[21,29,44,45] Also, race may influence susceptibility to herpes zoster, thus to subsequent PHN[6,40]; and individual genetic factors may prove important for specifically targeted treatment of neuropathic pain.[38] Therefore, studying relationships among patient demographics, disease characteristics, pain severity, and corresponding levels of pain interference with daily activities can identify factors important for multidimensional treatment of PHN in clinical practice.

Although there are a number of publications describing risk factors for PHN as well as factors that affect pain experience, comprehensive analyses on how various baseline characteristics can influence PHN treatment outcomes have not been performed. Therefore, the goal of the current, secondary analysis of integrated data from the phase 3 and 4 studies of G-GR was to better understand how patient characteristics and key patient-reported outcome measures relate to patients' overall well-being after treatment with G-GR. Such comprehensive analysis may identify factors important for multidimensional responses to treatment that can potentially inform the design and evaluation of treatment strategies for better management of PHN.

Methods

Patients

Data from patients treated with G-GR in 2 phase 3, double-blind, randomized, placebo-controlled studies (81-0045 and 81-0062) and 1 phase 4, open-label, single-arm study (81-0067) were integrated before this analysis. Patients treated with placebo in phase 3 studies were not included in this analysis because this would have resulted in uneven G-GR versus placebo patient populations. Also, various exploratory analyses of integrated data from phase 3 studies for differences between patients treated with G-GR and patients treated with placebo were published previously.[10,12,17,18,33]

The main patient inclusion criteria for the phase 3 studies were age ≥18 years with neuropathic pain for ≥3 months (81-0045) or ≥6 months (81-0062) after the healing of herpes zoster skin rash; and an average daily pain score of ≥4 based on an 11-point Likert scale (where 0 = no pain and 10 = worst possible pain), at the end of a 1-week pretreatment baseline period. Main exclusion criteria included previous lack of response to treatment with ≥1200 mg/day gabapentin or ≥300 mg/day pregabalin; dose-limiting adverse events with gabapentin or hypersensitivity to gabapentin; use of any concomitant medication excluded by the inclusion criteria (including capsaicin, opiates, topical lidocaine, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors); and creatinine clearance (CrCl) <50 mL/min. For the phase 4 study, patients were relatively unselected to reflect the real-world population, and included patients ≥18 years with active PHN, regardless of their baseline pain scores. Exclusion criteria were limited to those in the product label: pregnant women or nursing mothers, patients with hypersensitivity to gabapentin, and patients who had an estimated Cr/Cl <30 mL/min or who were on hemodialysis. There were no restrictions on the use of prior medications in the phase 4 study, and the use of concomitant neuropathic pain medication was permitted.

Treatments

All 3 studies shared a similar G-GR treatment schedule. Patients were titrated to 1800 mg/day G-GR over 2 weeks, followed by 8 weeks (phase 3) or 6 weeks (phase 4) of

stable dosing with G-GR 1800 mg taken once daily with the evening meal. Therefore, the end of the study in the current analysis was defined as week 10 for the phase 3 studies and week 8 for the phase 4 study. The 2-week titration period used a set schedule: day 1, 300 mg; day 2, 600 mg; days 3–6, 900 mg; days 7–10, 1200 mg; days 11–14, 1500 mg; day 15, 1800 mg. The schedule for 1-week dose tapering was 2 × 600 mg for 3 days and 1 × 600 mg for the last 4 days.

Efficacy Evaluations

Efficacy assessments common for phase 3 and 4 studies, and thus used in the current secondary analysis, were the VAS for the assessment of pain intensity on the 100-mm scale, the BPI for the assessment of pain qualities and pain interference on the 0–10 Numerical Rating Scale (NRS; where 0 = no pain interference and 10 = worst possible pain/interference), and the Clinical/Patient Global Impression of Change (C/PGIC) for the assessment of overall improvement. On the BPI, changes in patients' perceived pain (worst, least, average, and current pain) and the degree to which their pain interfered with their life and activities (general activity, mood, walking ability, normal work, relationship, sleep, enjoyment of life, and the average of 7 interference scores) were measured. On the CGIC or PGIC, the proportion of patients categorized as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse" was determined. VAS and BPI were completed at baseline, at week 2 (end of titration), and at the end of the study (week 10 for phase 3 and week 8 for phase 4). CGIC and PGIC were completed at the end of the study.

Statistical Methods

To remain compliant with clinical trials, patient populations and statistical methods were largely based on FDA-approved statistical plans of the individual phase 3 and 4 studies.[25,37,43] Patients who took ≥1 dose of G-GR, had a valid baseline measurement, and completed ≥1 post-baseline efficacy assessment (intent-to-treat [ITT] populations in the individual studies) were included in the efficacy population. Patients who completed each individual study (10 weeks of treatment in phase 3 and 8 weeks of treatment in phase 4) were included in the completer population.

Mean (standard error of the mean [SEM]) changes from baseline to the end of the study in the VAS and BPI scores, and the proportion of patients categorized on the CGIC and PGIC at the end of the study were determined. Changes from baseline in the VAS and BPI interference scores were estimated with an analysis of covariance model that included treatment, study centers, and the baseline value as covariates. Missing data were imputed by the last observation carried forward method. In agreement with the published literature and the consensus summary statement produced by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,[7,9,30] reductions of ≥30% from baseline until the end of the study served as determinants of clinically important reductions in the VAS or BPI scores (VAS or BPI responders). PGIC responders were defined as patients who reported feeling "much" or "very much" improved at the end of G-GR treatment, whereas PGIC nonresponders were defined as patients who did not (ie, patients in all other PGIC categories).

To evaluate the degree of a linear relationship among percent changes in efficacy variables, bivariate correlation analyses with calculation of the coefficient of determination (R^2) were performed. For the bivariate correlation analyses, changes in PGIC or CGIC were calculated by coding each category from 1 to 7, with "no change" treated as the baseline value. Multivariable, continuous regression analyses were performed to evaluate predictive factors for percent changes in VAS and BPI, with regression coefficient (standard error [SE]) for the rate of change of a conditional mean of the dependent variable (response variable), and with the coefficient *P* value for the significance of the independent variable (predictor). Multivariable, logistic regression analyses were performed to evaluate predictive factors for being "much" or "very much" improved on the CGIC or PGIC, with the odds ratio (OR) for the change in the log odds of the dependent variable per unit change in the independent variable, and the *P* value for the significance of the predictor. Each regression analysis was performed twice: 1) with patient demographics (age, sex, and race) as independent variables, and 2) with patient demographics plus the VAS and BPI scores at baseline (to test the role of baseline disease characteristics in influencing treatment outcomes) and at week 2 (to test the role of early response in influencing treatment outcomes) as independent variables. These independent variables were common for phase 3 and 4 trials and were chosen based on our knowledge of various variables that can potentially influence treatment outcomes; these included risk factors for developing PHN, herpes zoster, and other pain syndromes,[6,21,29,38,40,44,45] as well as known factors differentially associated with the experience of pain.[8,26,34] A positive regression coefficient or OR indicated that scores on the 2 items changed in the same direction, and a negative coefficient or OR indicated that scores on the 2 items changed in opposite directions. *P* values were calculated using a paired, 2-tailed t-test, and statistical significance was set at $P \leq .05$. Correlation and regression analyses were performed on the efficacy population and, to validate the results, on the completer population. To test how well different items measured the same idea and whether the analysis delivered reliable scores, internal consistency reliability with calculation of coefficient of consistency (Cronbach's alpha) was performed for correlation analyses.

Results

Baseline Characteristics

In the phase 3 studies, 721 patients were randomized to receive G-GR or placebo, and 359 patients received

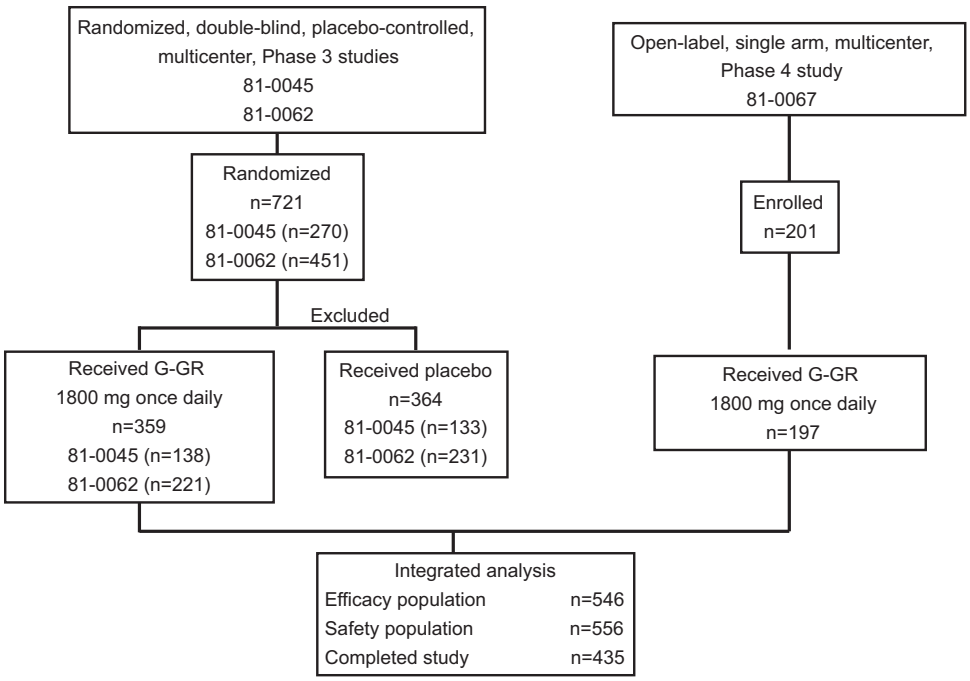

Figure 1. Patient disposition.

≥1 dose of G-GR 1800 mg (Fig 1). Patients who received placebo were not included in the current analyses. In the phase 4 study, 201 patients were enrolled, and 197 received at least 1 dose of G-GR 1800 mg. For the current integrated analyses, 546 patients were dosed with G-GR and were included in the efficacy population, and 435 (79.7%) patients completed the study and were included in the completer population (Fig 1).

The mean (SD) age of all patients was 66.7 (12.9) years, and 64.4% of patients were ≥65 years of age (Table 1). The majority of patients were female (60.3%) and white (86.2%). Mean baseline pain intensity on the 100-mm VAS was 62.2 (Table 2). The highest mean BPI interference scores at baseline, measured on the 0–10 NRS, were for worst pain (7.0), average pain (5.7), and current pain (5.4), as well as sleep interference (5.1) and enjoyment of life (5.0) (Table 2). The lowest BPI mean scores at baseline were for walking ability (2.9) and for relationship (3.3). The BPI average interference score at baseline was 4.2.

Table 1. Patient Demographics

	G-GR 1800 MG/DAY (N = 556)
Age, y	
Mean (SD)	66.7 (12.9)
Median	69.0
(Min, max)	(18.0, 92.0)
Age category, n (%)	
<55 y	89 (16.0)
55–64 y	109 (19.6)
65–74 y	195 (35.1)
≥75 y	163 (29.3)
Sex, n (%)	
Female	335 (60.3)
Male	221 (39.7)
Race, n (%)	
White	479 (86.2)
Hispanic or Latino	38 (6.8)
African American	29 (5.2)
Asian	6 (1.1)
Other	4 (.7)

Efficacy Measurements at the End of Treatment

For the measurement of pain intensity using VAS, the mean reduction from baseline to the end of G-GR treatment was −24 ($P < .0001$) (Table 3). For the measurement of pain qualities using the BPI scale, the mean change from baseline in the worst pain (−2.4), average pain (−1.9), current pain (−2.1), and least pain (−1.5) scores in the last 24 hours were statistically significant ($P < .0001$) (Fig 2A). The mean reduction from baseline to the end of treatment in all 7 individual types of BPI interference as well as in the average interference score was also statistically significant ($P < .0001$) (Fig 2B).

According to the PGIC, the largest group of patients (45.2%) felt "much" or "very much" improved at the end of the G-GR treatment; 21.6% of patients reported feeling "minimally" improved, and 24.5% of patients reported "no change" (Fig 3). The proportion of patients improved on the CGIC was similar, with 47.2% of patients feeling "much" or "very much" improved at the end of G-GR treatment (Fig 3).

Correlation

For patients in the efficacy population treated with G-GR, there were wide-ranging, significant (indicated by $P \leq .05$ for the difference of R^2 values from 0), positive

Table 2. Baseline Disease Characteristics

	G-GR 1800 MG/DAY (N = 546)
VAS	
Mean (SD)	62.2 (18.8)
95% CI	60.6, 63.8
Min–max	2–100
BPI worst pain	
Mean (SD)	7.0 (1.8)
95% CI	6.9, 7.2
Min–max	0–10
BPI least pain	
Mean (SD)	4.0 (2.3)
95% CI	3.8, 4.2
Min–max	0–10
BPI average pain	
Mean (SD)	5.7 (1.8)
95% CI	5.6, 5.9
Min–max	0–10
BPI current pain	
Mean (SD)	5.4 (2.36)
95% CI	5.2, 5.6
Min–max	0–10
BPI general activity	
Mean (SD)	4.5 (2.8)
95% CI	4.3, 4.8
Min–max	0–10
BPI mood	
Mean (SD)	4.7 (2.9)
95% CI	4.5, 5.0
Min–max	0–10
BPI walking ability	
Mean (SD)	2.9 (3.1)
95% CI	2.6, 3.2
Min–max	0–10
BPI normal work	
Mean (SD)	4.1 (3.0)
95% CI	3.9, 4.4
Min–max	0–10
BPI relationship	
Mean (SD)	3.3 (2.9)
95% CI	3.0, 3.5
Min–max	0–10
BPI sleep interference	
Mean (SD)	5.1 (2.9)
95% CI	4.9, 5.4
Min–max	0–10
BPI enjoyment of life	
Mean (SD)	5.0 (3.0)
95% CI	4.7, 5.2
Min–max	0–10
BPI average interference score	
Mean (SD)	4.2 (2.4)
95% CI	4.0, 4.4
Min–max	0–10

Abbreviation: CI, confidence interval.

(indicated by all R^2 larger than 0) correlations among percent reductions from baseline to the end of treatment in the efficacy variables (VAS, BPI, CGIC, and PGIC) (Fig 4A). Generally, correlations among percent changes in pain scores on the VAS and BPI pain (worst, least, average, and current pain) were stronger (indicated by R^2 values) than those between changes in the

Table 3. Pain Intensity Measured on the VAS at the End of the Study

	G-GR 1800 MG/DAY (N = 546)
End of study	
Mean (SD)	37.5 (25.6)
95% CI	35.3, 39.6
Median	34.0
Min–max	0–98.0
Change from baseline	
Mean (SD)	−24.6 (26.2)
95% CI	−26.8, −22.4
Median	−23.0
Min–max	−93.0–58.0
P value*	<.0001

Abbreviation: CI, confidence interval.
**P* value for the difference from baseline is from the Wilcoxon signed rank test.

VAS/BPI pain and BPI interference (general activity, mood, walking ability, normal work, relationship, sleep, enjoyment of life, average) scores. Similarly, correlations among percent changes in the BPI interference scores were stronger than those between changes in the BPI interference and VAS/BPI pain scores. The correlation between improvements on the PGIC and percent changes in other efficacy variables was significant and of moderate strength, whereas the correlation between CGIC and other efficacy variables was weak and partially significant (Fig 4A).

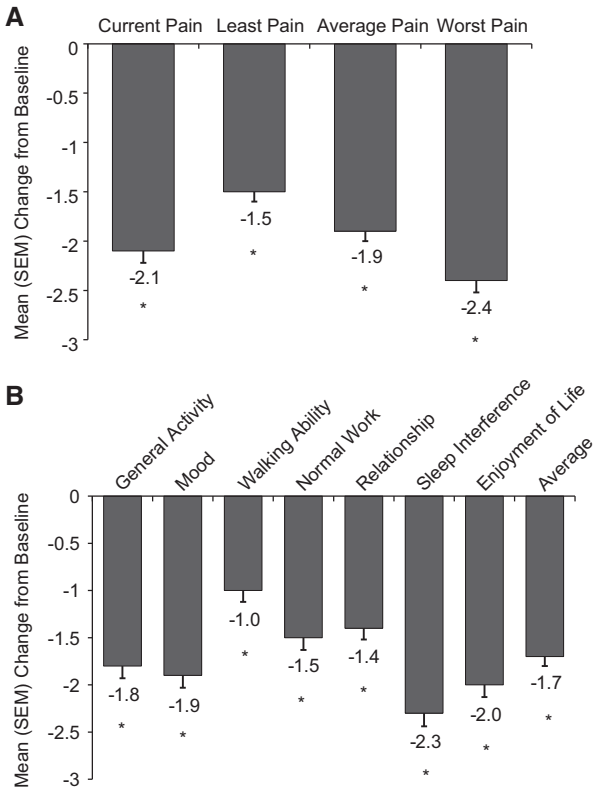

Figure 2. Change from baseline in BPI scores. **(A)** Mean (SEM) change from baseline in BPI pain scores. **(B)** Mean (SEM) change from baseline in BPI interference scores. **P* < .0001 for the difference from baseline.

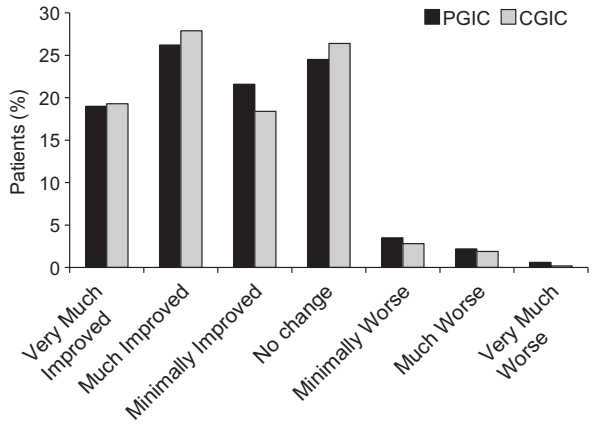

Figure 3. Proportion of patients improved on the PGIC and CGIC.

To test whether these correlations were of clinical significance, the analysis was performed for 3 patient groups: 1) VAS responders versus nonresponders (those with ≥30% reductions in the VAS score versus <30% reductions), 2) BPI average interference responders versus nonresponders (those with ≥30% reductions in the BPI average interference score versus <30% reductions), and 3) PGIC responders versus nonresponders (patients "much" or "very much" improved versus patients in all other PGIC categories). Generally, for VAS responders (Fig 4B) or BPI average interference responders (Fig 4C), the correlation among percent changes in various efficacy variables was stronger (indicated by larger R^2 values) and more correlations were significant compared with nonresponders. In contrast, there was little difference between PGIC responders and PGIC nonresponders for percent changes in various efficacy variables (Fig 4D). The correlation between improvements on the PGIC and percent reductions in other efficacy variables was the weakest for PGIC responders (compare Figs 4B and 4C with 4D), whereas the correlation between PGIC/CGIC and other efficacy variables was the strongest for BPI average interference responders (Fig 4C).

Internal consistency values demonstrated strong internal consistency: standardized Cronbach's alpha was .9473 for analyses among all patients in the efficacy population; it was .9363 for analyses among VAS responders and .8927 for analyses among VAS nonresponders; it was .9039 for analyses among BPI average interference responders and .8672 for analyses among nonresponders; it was .9179 for analyses among PGIC responders and .9066 for analyses among nonresponders.

To validate the results obtained for the efficacy population (ITT populations from individual studies), correlation analyses in the completer population (patients treated with G-GR who completed individual studies) were performed. The strength, significance, and profile of correlations among efficacy variables for the completer population were similar to those for the efficacy population (Supplementary Fig 1).

Predictive Factors

To identify predictive factors for percent changes in the VAS and BPI scores, as well as for being "much" or "very much" improved on the CGIC or PGIC, multivariable regression analyses with patient demographics (sex, age, and race) as independent variables were performed. Sex and age, but not race, were significant predictors for percent changes in pain measures on the VAS and BPI (but for changes in BPI interference scores), and for being improved on the CGIC or PGIC (Table 4). Males were more likely to report changes on the VAS and the BPI average pain scores than were females. Older patients (≥75 years) were more likely to report changes in the BPI least pain score than younger patients (<75 years). Females and older patients were more likely to report feeling "much" or "very much" improved on the CGIC or PGIC.

To determine the magnitude of patient demographics in predicting responses to treatment, we also included VAS and BPI scores at baseline (baseline disease characteristics) and at week 2 (early response to treatment) as factors in the regression model. When adjusted for VAS and BPI scores, patient demographics were not significant predictors of percent changes in the VAS and BPI scores at the end of G-GR treatment (Table 5). VAS or BPI scores at baseline were negative predictors and scores at week 2 were positive predictors of percent changes from baseline to the end of the study in corresponding VAS or BPI variables (Table 5). Besides the baseline and week 2 VAS scores, the only other predictor of percent changes in VAS was the BPI average pain score at baseline. Among all BPI interferences scores, the only significant predictor for percent changes in the BPI worst, average, and current pain was the BPI sleep interference score at week 2. For predictors of changes in various interference scores, the BPI worst pain score at baseline was the predictor of percent changes in the BPI general activity, mood, sleep interference, and enjoyment of life scores. BPI current pain at baseline or at week 2 was also a common predictor of percent changes in BPI general activity, mood, enjoyment of life, and additionally of normal work. Neither of the most common predictors of changes in various BPI interference scores significantly predicted percent changes in the BPI average interference score; instead, the BPI sleep interference score at baseline was of highest significance (Table 5).

For predictors of overall improvement, the VAS scores at baseline and at week 2 were common significant predictors of "much" or "very much" improvement on the CGIC or PGIC (Table 5). For being "much" or "very much" improved on the CGIC, the only other predictive factor was sex; females were more likely to report improvements on the CGIC than males. Other than the VAS scores, there were 4 more significant predictors of being "much" or "very much" improved on the PGIC, and these included BPI current pain at week 2, BPI normal work and relationship at baseline, and age (with older patients more likely to report improvement than younger patients).

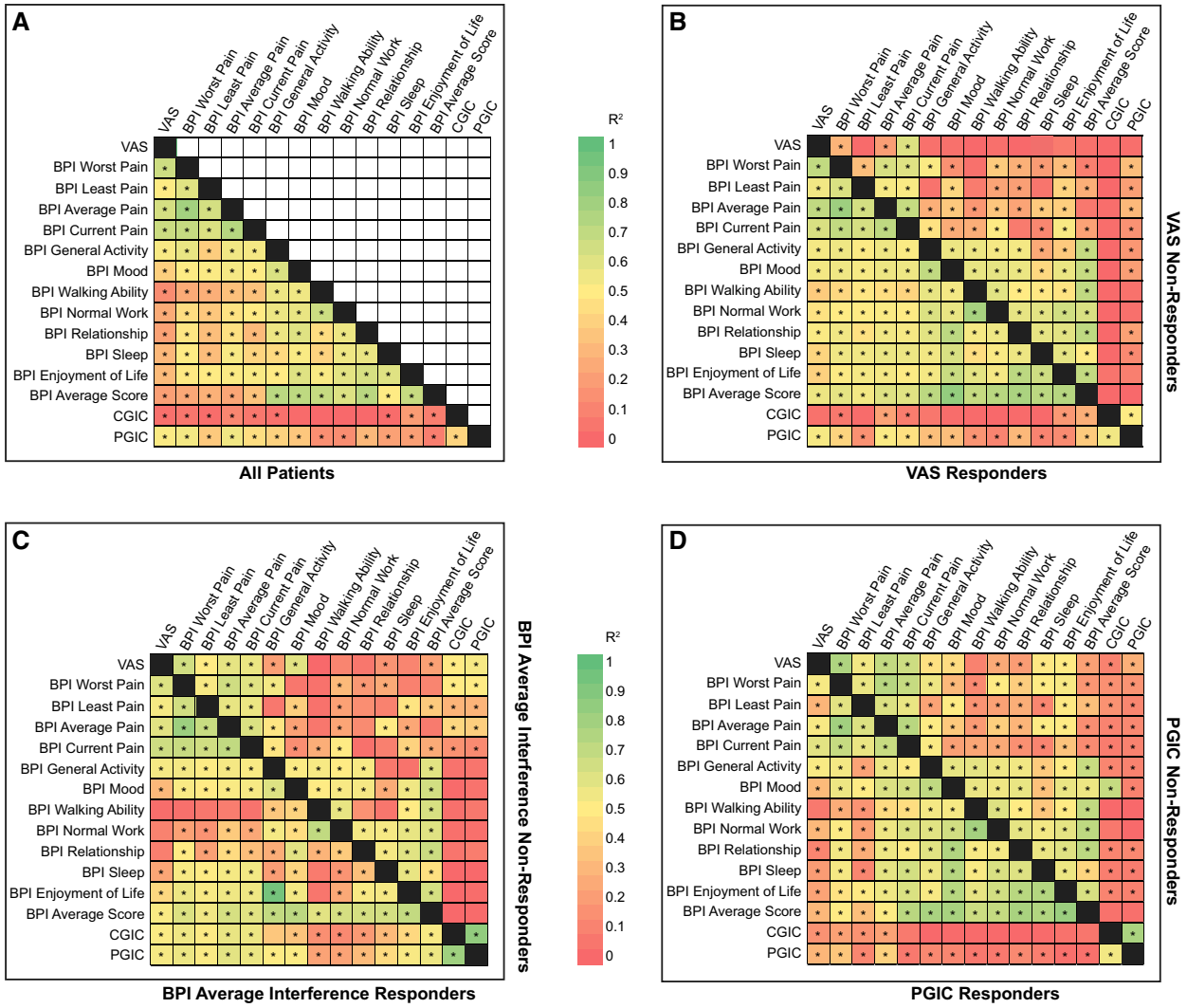

Figure 4. Correlations among percent changes in efficacy measures. The coefficient of determination (R^2) was calculated for **(A)** all patients in the efficacy population; **(B)** VAS responders (patients with ≥30% reduction in VAS) versus VAS nonresponders (patients with <30% reduction in VAS); **(C)** BPI average interference responders (patients with ≥30% reduction in BPI average interference) versus BPI average interference nonresponders (patients with <30% reduction in BPI average interference); and (**D**) PGIC responders (patients feeling "very much" or "much" improved) versus PGIC nonresponders (patients not feeling "very much" or "much" improved). Green indicates the strongest, yellow the intermediate, and red the weakest correlation. *$P \leq .05$ for the difference from 0.

Predictive factors for the completer population were analyzed to validate the results in the efficacy population, and the results were similar to those presented above (Supplementary Tables 1 and 2). The most prominent difference was that BPI sleep interference scores at baseline or at week 2 were even more common predictors of percent changes in pain qualities; sleep interference scores were among predictors for changes in all BPI pain scores as well as for changes in the VAS.

Discussion

Neuropathic pain in general, and PHN in particular, is associated with poor patient-reported quality of life,[4,20,31] but few studies have examined the impact of pain relief on patient function or how key patient-reported outcomes influence each other,[15,41,42] and even fewer have comprehensively analyzed relationships among efficacy outcomes, patient demographics, and disease characteristics. This study of patients with PHN treated with once-daily G-GR provides in-depth insight into how key patient and disease characteristics may influence the effectiveness of treatment, and describes complex interactions among reductions in pain intensity, interference of pain with various aspects of patient function, and overall improvement. The evidence presented may support better understanding of the results of clinical trials, thus leading to more successful transition to real-world clinical practice.

This study demonstrated wide-ranging positive correlations among changes in self-reported pain intensity, changes in self-reported daily functioning, and in the impression of overall improvement. We also found that correlations among changes in measures of pain intensity on the VAS and BPI scales were generally stronger than correlations between changes in pain intensity and pain interference on the BPI inference scale. Similarly, correlations among changes in various measures

Table 4. Patient Demographics as Predictors of Changes in Efficacy Measures at the End of G-GR Treatment

Dependent Variable	*Predictive Factor*	*Coefficient (SE)*	P *value*
Percent change in VAS	Sex (female vs male)	−9.86 (4.35)	.0239
Percent change in BPI least pain	Age (≥75 years vs <75 years)	13.40 (6.33)	.0346
Percent change in BPI average pain	Sex (female vs male)	−7.50 (3.75)	.0459
Dependent Variable	*Predictive Factor*	*OR (95% CI)*	P *value*
"Much" or "very much" improved on CGIC	Sex (female vs male)	1.78 (1.25, 2.53)	.0015
	Age (≥75 y vs <75 y)	.57 (.39, .84)	.0047
"Much" or "Very Much" improved on PGIC	Sex (female vs male)	1.61 (1.13, 2.29)	.0088
	Age (≥75 y vs <75 y)	.60 (.41, .89)	.0100

Abbreviation: CI, confidence interval.

of pain interference were stronger than those between changes in pain interference and pain intensity. These results are consistent with previous studies showing that improvement in pain generally relates to improvement in patient function[31,36]; however, at least to some degree, patients may differentiate between self-rated pain intensity and self-rated pain interference. Also, weaker intercorrelations between pain intensity and its interference compared with intracorrelations within pain intensity and within pain interference may be due to the fact that some patients can report clinically important changes in function without experiencing significant reductions in pain intensity.[15] In summary, such wide-ranging positive correlations suggest complex networked systems characterized by positive feedback loops, where treatment outcomes are in a reciprocal relationship. An example of such a reciprocal correlation is that between pain and sleep, where pain disturbs sleep, and poor sleep enhances pain.[23,35,39]

The strength and significance of these wide-ranging correlations among changes in efficacy end points were dependent on the clinical significance of reductions in pain intensity and pain interference because there were differences in the correlation profiles between patients with ≥30% versus <30% reduction in the VAS or BPI average interference (responders vs nonresponders). In contrast, patients divided into 2 groups based on their PGIC responses ("much" or "very much" improved vs not improved) showed similar correlations among efficacy end points, thus showing no dependence on responses measured on the PGIC. These results suggest a potentially unique role of assessments of the overall improvement on the PGIC, showing associations among treatment outcomes for patients reporting both clinically significant and not significant improvements on the PGIC. The relationship between PGIC and other efficacy measures should be further investigated, at the level of single variables, to characterize the impact of assessments on the PGIC in more detail.

Correlation does not generally imply causation, and we found that despite wide-ranging correlations among VAS, BPI, CGIC, and PGIC scores, the influence of these variables on each other was somewhat selective. Changes in each individual measure of pain interference assessed on the BPI had distinct predictive factors, with only a few measures being a common predictor of change in another measure of pain interference. These included the BPI sleep interference scores at baseline (baseline disease characteristic) and at week 2 (early response to treatment) as common predictors of changes in most BPI pain scores and the strongest predictor of changes in the average of the 7 BPI interference scores. In contrast, the overall impression of improvement at the end of G-GR treatment reported either by patients (PGIC) or by clinicians (CGIC) appeared to be influenced by patients' experiencing pain relief rather than by patients experiencing reductions in the interference of pain with their functioning; pain intensity scores on the VAS were predictors of highest significance for being "much" or "very much" improved on the PGIC or CGIC. In summary, the results of both predictor and correlation analyses identified potentially distinctive roles of certain efficacy end points, which may play an important role in the successful outcome of PHN treatment. Pain relief was not the only element contributing to successful PHN treatment, and assessments of pain interference with sleep on the BPI, and overall improvement on the PGIC in particular, seemed co-strategic factors. Also, as many trials on neuropathic pain, including PHN, have recently failed or showed only moderate treatment effects, it can be argued that, in addition to standard primary end points of measures of pain intensity, other co-primary end points should be considered, possibly assessments of sleep quality and overall improvement.[27,32] This could not only improve detection of true positive efficacy responses in trials of PHN and other neuropathic pain syndromes but also guide successful transition to real-world clinical practice.

The results of analyses that were performed on the integrated efficacy population (ITT populations from individual studies) were validated and confirmed by the analyses on the completer population (patients who completed each individual study). The strength and pattern of correlation among efficacy outcomes as well as the profile of predictors of changes in efficacy end points were similar in the completer population compared with those obtained for the efficacy population. Noticeably, the role of BPI sleep interference scores at baseline or at week 2 in predicting changes in pain intensity on

Table 5. Patient Demographics and Efficacy End Points as Predictors of Changes in Efficacy Measures at the End of G-GR Treatment

Dependent Variable	*Predictive Factor*	*Coefficient (SE)*	P *value*
Percent change in VAS	VAS at baseline	−1.25 (.17)	<.0001
	VAS at wk 2	.64 (.15)	<.0001
	BPI average pain at baseline	5.38 (2.08)	.0099
Percent change in BPI worst pain	BPI worst pain at baseline	−7.58 (1.48)	<.0001
	BPI worst pain at wk 2	3.46 (1.32)	.0088
	BPI average pain at wk 2	4.36 (1.71)	.0113
	BPI sleep interference at wk 2	−2.25 (.89)	.0117
	VAS at wk 2	.24 (.12)	.0460
Percent change in BPI least pain	BPI least pain at baseline	−13.22 (2.14)	<.0001
	BPI least pain at wk 2	7.05 (2.24)	.0017
	BPI average pain at wk 2	7.012 (2.88)	.0153
	BPI relationship at baseline	−3.26 (1.61)	.0432
Percent change in BPI average pain	BPI average pain at baseline	−7.77 (1.75)	<.0001
	BPI sleep interference at wk 2	−2.58 (.93)	.0057
	BPI average pain at wk 2	4.70 (1.79)	.0089
	VAS at wk 2	.28 (.12)	.0244
Percent change in BPI current pain	BPI current pain at baseline	−12.33 (2.12)	<.0001
	BPI current pain at wk 2	6.15 (1.98)	.0020
	BPI sleep interference at wk 2	−3.22 (1.54)	.0370
Percent change in BPI general activity	BPI general activity at baseline	−10.66 (2.21)	<.0001
	BPI average pain at wk 2	10.04 (3.15)	.0015
	BPI current pain at wk 2	5.30 (2.00)	.0084
	BPI least pain at baseline	5.51 (2.19)	.0123
	BPI relationship at wk 2	4.73 (2.02)	.0196
	BPI least pain at wk 2	−5.04 (2.44)	.0399
	BPI general activity at wk 2	3.86 (1.98)	.0517
	BPI worst pain at baseline	−5.27 (2.74)	.0549
Percent change in BPI mood	BPI mood at baseline	−11.37 (2.26)	<.0001
	Sex (female vs male)	16.54 (6.09)	.0069
	BPI worst pain at baseline	6.97 (2.83)	.0141
	BPI current pain at wk 2	4.94 (2.11)	.0198
	BPI relationship at wk 2	4.39 (2.12)	.0387
	BPI walking ability at baseline	3.77 (1.87)	.0444
Percent change in BPI walking ability	BPI walking ability at baseline	−9.71 (2.86)	.0008
	Sex (female vs male)	21.72 (9.14)	.0182
	BPI relationship at wk 2	7.13 (3.20)	.0266
	BPI walking ability at wk 2	5.63 (2.88)	.0515
Percent change in BPI normal work	BPI normal work at baseline	−13.99 (2.97)	<.0001
	BPI current pain at baseline	−7.48 (2.89)	.0100
	BPI current pain at wk 2	5.73 (2.77)	.0391
Percent change in BPI relationship	BPI relationship baseline	−19.50 (2.87)	<.0001
	BPI relationship at wk 2	10.26 (3.22)	.0016
	BPI walking ability at wk 2	−7.19 (2.77)	.0097
	BPI walking ability at baseline	5.81 (2.56)	.0237
	BPI least pain at baseline	6.53 (3.16)	.0394
	BPI general activity at baseline	6.55 (3.33)	.0498
Percent change in BPI sleep interference	BPI sleep interference at baseline	−8.03 (1.77)	<.0001
	BPI average pain at baseline	−8.14 (3.15)	.0102
	BPI worst pain at baseline	6.68 (2.79)	.0170
	BPI least pain at wk 2	6.05 (2.57)	.0190
	BPI average pain at wk 2	7.37 (3.21)	.0220
	BPI sleep interference at wk 2	3.74 (1.69)	.0278
Percent change in BPI enjoyment of life	BPI enjoyment of life at baseline	−14.02 (2.27)	<.0001
	BPI enjoyment of life at wk 2	7.00 (2.25)	.0020
	BPI current pain at baseline	−6.89 (2.45)	.0052
	BPI worst pain at baseline	7.14 (3.24)	.0283
	BPI average pain at wk 2	8.16 (3.79)	.0319

Table 5. Continued

Dependent Variable	Predictive Factor	Coefficient (SE)	P value
Percent change in BPI average interference score	BPI sleep interference at baseline	−8.32 (3.38)	.0140
	BPI walking ability at wk 2	8.64 (4.24)	.0418
	BPI general activity at baseline	−8.90 (4.54)	.0505

Dependent Variable	Predictive Factor	OR (95% CI)	P value
"Much" or "very much" improved on CGIC	VAS at wk 2	.97 (.95, .99)	.0002
	VAS at baseline	1.03 (1.01, 1.05)	.0046
	Sex (female vs male)	1.58 (1.03, 2.40)	.0346
"Much" or "very much" improved on PGIC	VAS at wk 2	.97 (.96, .99)	.0007
	VAS at baseline	1.03 (1.01, 1.05)	.0045
	BPI current pain at wk 2	.82 (.71, .95)	.0102
	BPI normal work at baseline	1.19 (1.02, 1.39)	.0279
	BPI relationship at baseline	1.17 (1.01, 1.34)	.0353
	Age (≥75 y vs <75 y)	.61 (.38, .97)	.0364

Abbreviation: CI, confidence interval.

the VAS and pain qualities on the BPI was even more prominent for the completer population. The analyses performed on both the efficacy and completer populations described an important role of pain intensity in influencing the overall impression of improvement in patients with PHN, and of the sleep interference score in influencing changes in both VAS/BPI pain and the BPI average of interference scores. These results highlight a key relationship between pain intensity and sleep interference, and their important role in influencing patient functioning. This observation is consistent with the well-described reciprocal relationship between pain and sleep,[23,35,39] and provides further evidence on the role of pain-sleep interaction on other treatment outcomes. Further analyses of the relationship between pain and sleep, and their impact on overall improvements, can provide clinically relevant evidence for more comprehensive understanding of successful treatment of PHN, and possibly other neuropathic pain syndromes.

Because of known sex differences in pain perception, with females generally reporting higher average pain scores than males,[36] and because of age-related modifications in pain perception,[24] sex and age were expected to be important factors influencing changes in pain intensity and in other measures of treatment outcomes. However, in this study, these 2 factors did not appear to play an important role in influencing changes in patient-rated efficacy measures for both the efficacy and completer populations, especially when analyses were adjusted for disease characteristics and early responses to treatment (efficacy measures at baseline and at week 2). These results imply that pain intensity and to what degree it interferes with daily activities play the key role in influencing treatment outcomes, independent of patients' age or sex. This observation is consistent with the previous analysis in patients with PHN treated with G-GR in the phase 3 clinical program that showed that treatment outcomes and tolerability were independent of age.[12] Thus, for future analyses of complex relationships, it may be important to consider patient demographics together with other characteristics (eg, disease characteristics and early responses to treatment) for a more accurate picture of the role of each variable.

Possible limitations of the analysis presented here include the fact that changes in pain intensity and pain interference may simply be influenced by high baseline scores in respective variables. However, baseline values were negative (ie, scores on the 2 items change in opposite directions) predictors of percent changes in corresponding efficacy variables for pain intensity or pain interference. This indicates that high baseline values did not simply result in big percent changes in outcome measures at the end of G-GR treatment. Rather, patients' ability to detect change was influenced by the severity of their baseline disease characteristics. Another factor that could potentially limit or complicate understanding of relationships as analyzed in this study is the sample size. Because the sample size affects the regression and correlation analyses, the number of patients in each group should be well distributed, with no groups containing a small number of patients. In the current study, the number of white versus nonwhite patients was not well distributed (86% vs 14%), which might have contributed to the lack of significance of this demographic variable. Therefore, although informative, multivariable analyses should be carefully designed and interpreted to avoid drawing incorrect conclusions. Furthermore, as various scales were used to measure various treatment outcomes (ie, VAS, BPI pain and interference, PGIC, and CGIC), we observed a certain level of scale specificity; for example, changes from baseline in BPI interference scores were mostly influenced by scores in other BPI interference scores, and the correlation between the patient-rated PGIC and other patient-rated efficacy variables was stronger and of higher significance than the correlation between the clinician-rated CGIC and other patient-rated efficacy variables. These suggest that different scales for measurements of treatment outcomes and different sources of reporting might have affected the results of the current analysis to some degree, and these factors should be considered in such

comprehensive evaluations of relationships among treatment outcomes.

This was a unique and comprehensive analysis that provided an essential insight into how key efficacy measures and patient and disease characteristics influence patient-reported treatment outcomes. It revealed wide-ranging correlations among different efficacy outcomes in patients with PHN treated with once-daily G-GR. These complex correlations are most likely characterized by positive feedback loops in which pain interferes with patient functioning, and poor functioning enhances pain. Despite the wide-ranging correlations, the influence of efficacy variables on each other was selective and revealed a potentially important role of 3 factors: pain intensity, pain interference with sleep, and overall improvement at the end of G-GR treatment. Together, these results support a well-established reciprocal pain-sleep correlation, and demonstrate an important role of this interaction in influencing other treatment outcomes. Contrary to expectations, patient demographics did not play an important role, especially when other efficacy variables were included in the assessment, suggesting that perception of pain and its interference with daily activities was key for patients self-rating their treatment, independent of patients' age or sex.

In conclusion, factors characterized in this secondary analysis of phase 3 and 4 studies may contribute to better design and interpretation of clinical trials, with measures of sleep quality and overall improvements as potential co-primary end points, along with pain intensity, for improved detection of efficacy responses. Also, more comprehensive understanding of what factors lead to effective treatment outcomes will help guide successful management of PHN in real-world clinical practice. As PHN treatment remains difficult and often inadequate, such comprehensive analyses of interactions among efficacy, demographic, and disease characteristic variables from other clinical trials in PHN are needed for better understanding of the role of each factor, as well as for better comprehension of the limitations of such analyses, which will translate into accurate interpretation of the results, their successful transition to clinical practice, and thus better patient satisfaction with treatment.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpain.2015.08.011.

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